

## Urolithiasis

Lifetime risk of renal stone disease 10-15%

Peak incidence 30-50 years

Females have bimodal distribution – second peak after menopause

Males > females 2:1 [females have higher levels of urinary citrates; serum testosterone a/w higher production of hepatic oxalate]

Whites and asians > blacks and hispanics

More common in hot, dry climates, particularly those populated by fair-skinned races [KSA; UAE; USA; Canada; Japan are top five]

Risk factors intrinsic and extrinsic

Intrinsic gender, genetic and metabolic (see below)

Extrinsic climate, occupational, fluid intake (<1200 ml/day) and diet:

### Dietary Factors Influencing Urinary Stone-Formation

↑ Calcium	-	↑ Urinary calcium
↓ Calcium	-	↑ Urinary oxalate
↑ Oxalate	-	↑ Urinary oxalate
↑ Sodium	-	↑ Urinary calcium
↑ Refined sugars	-	↑ Urinary calcium
↓ Fibre	-	↑ Urinary calcium
↑ Fibre	-	↓ Urinary volume
↓ Magnesium	-	↓ Urinary magnesium

Water hardness (high calcium carbonate) controversial  
**Low urinary volume a/w inadequate intake is the single most common cause of stone formation in adults**

High animal protein causes high urinary oxalate, high urinary uric acid, low pH and low citrate (buffer used up) and high urinary calcium

Recurrence rate 50% at 10 yrs; 90% at 30 yrs

Risk factors for recurrent stone formation

Early age of onset

Strong family history

Type of stone

Cystine

Calcium hydrogen phosphate (Brushite)

Medical condition

Hyperparathyroidism

Hyperthyroidism

Sarcoidosis

Renal tubular acidosis

Primary hyperoxaluria

Cystinuria

Malabsorption

Crohn's disease

Jejunoileal bypass

Intestinal resection

**Drugs**

Indinavir and triamterene  
Vitamin D and megadose calcium supplementation

**Anatomical abnormality**

PUJO  
Calycceal diverticulum  
Medullary sponge kidney  
Horseshoe kidney

**Types**

## (i) Calcium stones (80%)

Calcium oxalate  
Calcium oxalate monohydrate\*  
Calcium oxalate dihydrate  
Calcium phosphate  
Hydroxyapatite (tricalcium diphosphate)  
Brushite\* (calcium hydrogen phosphate dihydrate)

## (ii) Infection stones (10-15%)

Magnesium ammonium phosphate  
Carbonate apatite

## (iii) Uric acid stones (5-10%)

Uric acid\*\*  
Ammonium urate  
Sodium urate

## (iv) Other (1%)

Cystine\*  
Xanthine\*\*  
Silica\*\*  
Indinavir//Triamterene\*\*

\* Cystine, calcium oxalate monohydrate, brushite hardest stones

\*\* Fully radiolucent, unlike cystine (ground-glass)

Chemical Type	Appearance
Calcium oxalate monohydrate	Hourglass
Calcium oxalate dihydrate	Envelope, tetrahedral
Calcium phosphate–apatite	Amorphous
Brushite	Needle shaped
Magnesium ammonium phosphate (struvite)	Rectangular, coffin-lid
Cystine	Hexagonal
Uric acid	Amorphous shards, plates

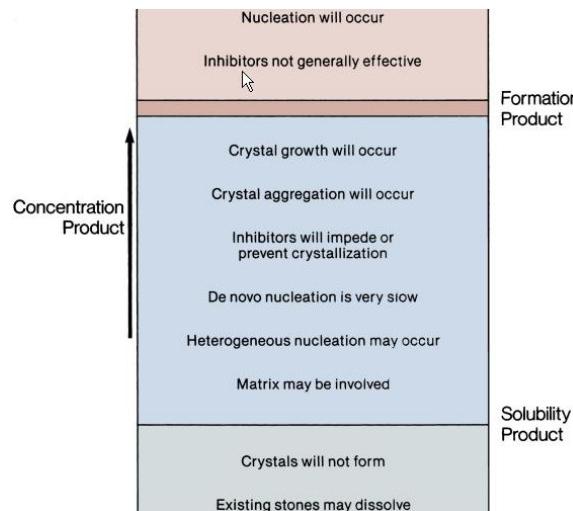
**Physicochemistry**

Relationship between salt and solute comprises 3 states: undersaturated, supersaturated but stable in solution (metastable), and supersaturated with spontaneous precipitation (unstable)

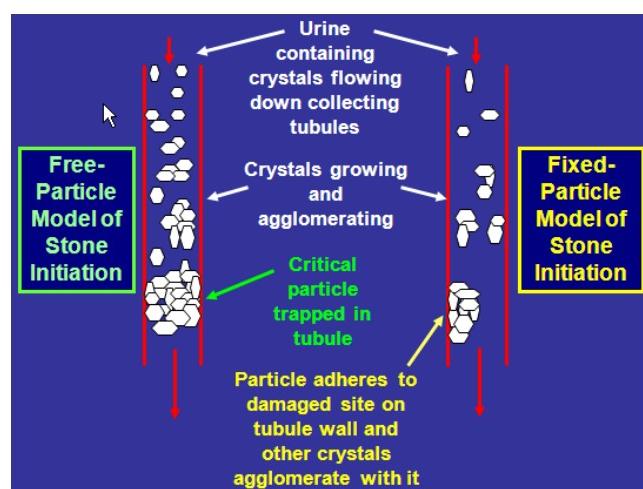
Concentration product = degree of saturation

Solubility product ( $K_{sp}$ ) = concentration of ions in a pure solution at which no more chemical will dissolve (without a change in pH, temp, or composition)

Formation product ( $K_f$ ) = the concentration product at which crystals actually form NB. For pure solutions  $K_{sp}$  effectively the same as  $K_f$ ; however in urine the presence of inhibitors allows a degree of metastable super-saturation.



Supersaturation alone produces crystals in static solutions but cannot explain formation in urine. Believed to occur through nucleation, aggregation and retention. Crystal nuclei either form in pure solutions (homogenous) or on existing surfaces (rbc, epithelial cell, debris). Individual crystals too small to grow sufficiently large to obstruct tubules within normal transit time. However if more than one clumps together may be retained in lumen and continue to grow (Free particle theory). Alternatively may attach to damaged tubular surfaces (Fixed particle theory)



Randall's plaques – subepithelial collection of calcified material at papilla; aetiology unknown. Arise within basement membrane of thin loops of Henle and extend through medullary interstitium to subepithelial location. Almost invariably composed of hydroxyapatite.

**Inhibitors**

Citrate	CaOx; CaPh
Magnesium	Ca Ox
Pyrophosphate	CaPh
Glycoproteins	
Nephrocalcin	CaOx
Tamm-Horsfall protein	CaOx
Uropontin (osteopontin)	CaOx

NB. All inhibit aggregation, but only nephrocalcin and uropontin inhibit nucleation and growth as well. There are no known urinary inhibitors of uric acid stones

**Promotors**

Polymerised THP
Matrix substance A

**Investigation of stone disease****First stone**

- U+E, Calcium, Urate
- Urinary dipstick (nitrites/leucocytes, pH, and cystine)
- pH > 7.5 suggests infection stones; pH < 5.5 uric acid stones
- Dipstick for cystine (sodium nitroprusside + urine = purple discolouration – Brandt's test)
- Stone analysis if possible
- Extended metabolic analysis not recommended in all patients because:
  - ~50% have a further stone at 10yrs
  - likelihood of recurrence not predicted by metabolic screening

**Recurrent stones – who to investigate?**

- Children
- Recurrent stone formers
- Bilateral stones
- Strong family history of stones
- Complex stones
- Stones in solitary kidney
- High likelihood on the basis of medical co-morbidity

**Recurrent stones – how to investigate?**

- U+E, calcium, urate, venous bicarbonate (?RTA)
- Urine
  - Random pH urine
  - Fasting pH urine
  - Dipstick for nitrites and leucocytes
  - Spot test for cystine
  - 2 x 24 hour urine collections:
    - #1- HCl (prevents precipitation of calcium salts; prevents oxidation of ascorbate to oxalate)
    - Citrate
    - Oxalate
    - Calcium
    - Creatinine/volume

Others optional (typically not routine)

Magnesium & phosphate used to determine supersaturation of calcium salts

Sodium, urea, phosphate and K<sup>+</sup> indicative of dietary habits

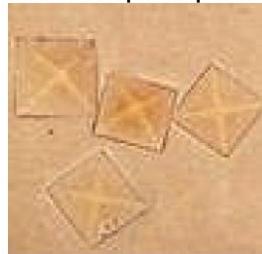
#2 – Sodium Azide (prevents precipitation of uric acid)

pH

uric acid

### **Calcium stone disease**

Account for ~80% stone episodes in UK [~50% calcium oxalate; ~30% calcium phosphate]



Calcium oxalate dihydrate crystals

#### Causes

90% idiopathic

10% metabolic abnormality

Hypercalcaemia

Hypercalciuria

Hyperoxaluria

Hyperuricosuria

Hypocitraturia

#### (i) Hypercalcaemia

Hyperparathyroidism; malignancy, TB, sarcoid (sarcoid granulomas produce 1,25(OH)<sub>2</sub>D<sub>3</sub> leading to absorptive hypercalciuria)

Incidence of calcium stone disease in hyperparathyroidism only 1%

Treatment of cause

#### (ii) Hypercalciuria

Isolated hypercalciuria in ~ 50% patients with CaOx stones

Defined as > 4mg/kg/24 hrs or >7mmol (men) or >6mmol

(women); Parks and Coe 1986. Other definition >200mg/day

Classification

Idiopathic (~50%)

Absorptive (from gut)

XS calcium absorption from gut – unknown cause

Increased filtration, reduced renal reabsorption (low PTH), raised phosphate, normocalcaemia, but fasting urinary calcium normal

Type 1 > 200mg/day on high or low ca diet

Type 2 > 200mg/day on high ca diet only

Renal leak

Impaired tubular resorption

Secondary hyperPTH, low phosphate, normocalcaemia, fasting calcium high

Resorptive (from bone)

Typically due to PTH or PTHrP  
 Hypercalcaemia, low phosphate, fasting urinary calcium high  
 Rx cause

	Absorptive	Renal	Resorptive
Serum calcium	Normal	Normal	Elevated
Parathyroid function	Suppressed	Stimulated (secondarily)	Stimulated (primarily)
Fasting urinary calcium	Normal	Elevated	Elevated
Intestinal calcium absorption	Elevated (primarily)	Elevated (secondarily)	Elevated (secondarily)

### Diagnosis

Resorptive hypercalciuria usually obvious: differentiation between idiopathic, renal and absorptive more difficult  
 Traditionally 'fast and load' calcium test – absorptive has normal fasting urinary calcium cf. resorptive/idiopathic  
 Fast and calcium load rarely performed as most patients get thiazides anyway

### Management

- a) **High fluid intake**
- b) Calcium restriction

Low ca diets a/w increased stone formation (due to increased oxalate absorption) Curhan 1993; 1997  
 Studies did not separate patients with absorptive hypercalciuria – moderate restriction may have a role in these patients

- c) Sodium cellulose phosphate

Binds divalent cations and reduces urinary calcium, even in type 1 hypercalciuria  
 No evidence reduces recurrence; a/w severe GI side effects, hyperoxaluria, hypomagnesaemia  
 Largely historical due to side effect profile

- d) **Thiazide diuretics**

Prevent sodium for calcium exchange in distal nephron.

Used for both renal and absorptive

Hydrochlorothiazide 25mg bd usual

Absorptive

Treats hypercalciuria, not cause

Previous studies have shown limited long-term efficacy (Preminger 1987). Initial increase in BMD indicating skeletal accretion, but after a variable period, bone stores overwhelmed and leak occurs again. Thiazide holiday recommended.

Renal

Ideal Rx as corrects underlying abnormality

No worries re. loss of effectiveness

Certainly reduces urinary calcium, but less impressive vs. recurrence (15% rec. vs. 27%)

controls) and only if taken for more than 2 yrs  
(?stone clinic effect)

Side effects problematic in 30%

Lethargy

Hypokalaemia}

Hypocitraturia }

**supplement with KCit**

Impotence

Reduced libido

Rarely pancreatitis

e) Orthophosphate

Uro-Phos-K

Slow release neutral potassium phosphate, binds intestinal calcium and inhibits activated vitamin D

Reduces urinary calcium and increases citrate but no evidence that reduces stone recurrence rates.

No publications since initial reports 1998

(iii) Hyperoxaluria

Dietary oxalic acid predominantly absorbed in colon

Oxalic acid completely filtered, secreted but not absorbed

Defined as > 40mg/day oxalate in urine

< 80mg/day = dietary hyperoxaluria; > 80mg/day enteric or primary hyperoxaluria

Causes:

Dietary hyperoxaluria

Reduce intake of rhubarb, tea, chocolate, nuts, spinach and strawberries

Eliminate megadoses of vitamin C

Enteric hyperoxaluria

Most common cause of hyperoxaluria

Malabsorption syndromes (Crohn's etc.)

Bile salts increase permeability of intestinal mucosa to oxalate and calcium soap formation results in increased free gut oxalate

? role for *oxalobacter formigenes*

Primary hyperoxaluria

Rare autosomal recessive disease

Mutated AGT (see appendix) leads to very elevated levels of urinary oxalate (>100mg/day), causing CaOx stone disease, nephrocalcinosis and renal impairment (liver and kidney transplant required)

Management

**High fluid intake**

**Low oxalate diet**

[High calcium/magnesium diet proposed to chelate bile salts but hypercalciuria and diarrhoea problematic]

(iv) Hyperuricosuria

Urinary uric acid > 600mg/day

Only abnormality in ~10% calcium oxalate stone formers

Causes include overingestion, xs production (gout, myeloproliferative disorders, and drugs (see uric acid stones)

pH <5.5 results in uric acid crystal precipitation, which act as nidus for CaOx crystal nucleation

Uric acid crystals also bind urinary inhibitors (GAGs)

Management

**High fluid intake**

**Allopurinol** (xanthine oxidase inhibitor) 300 mg/day irrespective of serum urate

**Potassium citrate**

(v) Hypocitraturia

Definition urinary citrate < 320mg/day

Implicated in up to 50% stone formers

Citrate reduces stone formation in 3 ways

Reduces free urinary calcium by complexing Ca+

Directly prevents spontaneous CaOx nucleation

Prevents aggregation of CaOx crystals

Typically reflects acid base balance; in metabolic acidosis tubular c citrate reabsorption increased

Common disorders a/w hypocitraturia include distal renal tubular acidosis (see appendix), chronic diarrhoea, ACEIs and thiazides  
(?intracellular acidosis)

Management

**High fluid intake**

**Potassium citrate**

**Infection stones**

Common

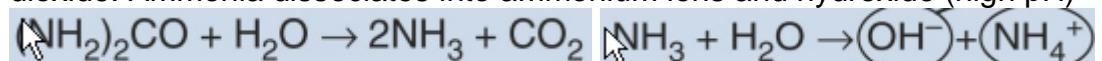
Account for 10-15% of all stones

Females > males 2:1

Composed predominantly of magnesium ammonium phosphate hexahydrate ( $Mg(NH_4)_2PO_4 \cdot 6H_2O$ ) with a variable component of carbonate apatite ( $Ca_{10}[PO_4]_6 \cdot CO_3$ ).

Caused by production of urease by bacteria (most commonly *Proteus mirabilis*, *Pseudomonas* and *Klebsiella* and *Staphylococcus* species)

Urease producing bacteria act on urea to produce ammonia and carbon dioxide. Ammonia dissociates into ammonium ions and hydroxide (high pH)



Ammonium ions then complex with magnesium and phosphate ions to form struvite – only occurs in alkaline environments pH > 7

Aetiology

Congenital abnormality

Impaired bladder emptying (neurogenic bladder)

Urinary diversion

Medical management

Limited

Antibiotics for acute infection, pre-operatively and following successful stone elimination in a patient with residual fragments

Hemacidrin for residual fragments a/w complications unless sterile urine

Acetohydroxamic acid (urease inhibitor 250mg tds) prevents new stones and reduced growth of pre-existing stones (Griffith 1991) but a/w low grade DIC and thrombosis and cessation rate up to 70%

### **Uric acid and urate stones**

5-10% of all renal stones

More common in middle east ? genetic susceptibility

Dalmatians, great apes and humans affected due to lack of uricase (converts uric acid to soluble allantoin for excretion by kidney)

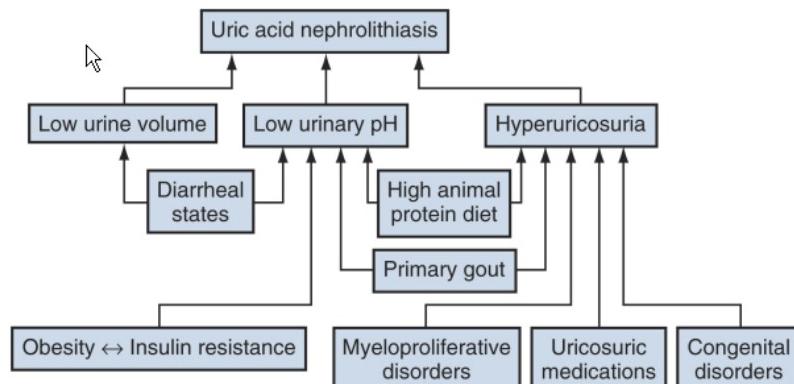
Uric acid solubility very pH dependent; below pH <5.5 significant reduction in uric acid solubility

Requirements for uric acid calculi formation:

Low urinary pH

Low urine volume

High relative uric acid concentration



### Aetiology

#### Low urinary pH

Most important factor, as most patients with uric acid stones have normal levels of urinary uric acid, but persistently low pH

Gouty diathesis\*, diarrhoea, gout and high animal protein intake

\*cause unknown but more common in patients with insulin resistance, possibly due to impaired urinary ammonia production

#### Low urine volume

Diarrhoea, ileostomies, poor oral intake, xs sweating

#### Hyperuricosuria

With hyperuricaemia (3):

primary gout (aetiology unknown);

myeloproliferative conditions

Lesch-Nyhan syndrome

Without hyperuricaemia (2)

drugs (salicylates, thiazides)

dietary (organ meats and sardines)

### Investigation

Urinary pH < 5.5

Elevated serum urate

24 hour urine collection (sodium azide) > 600mg/day  
 Negatively birefringent crystals on polarised light  
 Radiolucent calculus on plain imaging (also sodium urate, ammonium urate, xanthine, matrix, indinavir and triamterene)  
 Identifiable calculus on CT (350-400 Hounsfield units)

#### Management

##### **High fluid intake**

Dissolution therapy (chemolysis)

Sodium bicarbonate 500mg qds  
 Potassium citrate 20mEq tds  
 Occasionally intravenous 1/6 molar lactate or sodium bicarbonate solution used for patients with nausea and vomiting  
 Rarely intravesical or intrarenal sodium bicarbonate for direct chemolysis

#### Prevention

Allopurinol 300mg/day for all patients with hyperuricosuria (with or without hyperuricaemia) – not indicated in patients with merely low urinary pH or low volume  
 Allopurinol (xanthine oxidase inhibitor): side effects rare but include, rash, hypersensitivity (Stephens Johnson syndrome), hepatitis and renal failure

#### Ammonium urate stones

Rare in developed countries; common cause of endemic bladder stones in developing world

Typically form constituent of other stones but occasionally predominant component

A/w conditions of salt and water loss and low urinary pH; inflammatory bowel disease, laxative abuse and metabolic syndrome

Rx cause; alkali urine

#### Lesch Nyhan syndrome

Rare

Males only

X-linked hereditary defect of hypoxanthine-guanine phosphoribosyl transferase (HPRT)

Hyperuricaemia and hyperuricosuria

Choreoathetosis, mental retardation, self-mutilation, gouty arthritis and renal stones

#### **Cystine stones**



Relatively uncommon; accounts for 1-2% of renal stones (10% kids)

Autosomal recessive inheritance of defect in tubular resorption of 'COLA' amino acids (C=Cystine, O=Ornithine, L=Lysine, A=Arginine)

Mutations affect heteromeric amino acid transporters on chromosomes 2 and 19. Ornithine, lysine and arginine all highly soluble in urine; therefore only cystine a problem. Cystine more soluble at higher urinary pH and at higher ionic strengths (more dissolved salts)

Heterozygotes 1:200; Homozygotes 1:20,000, but some heterozygotes produce stones. Therefore incidence of symptomatic cystine stones 1:10,000

Median age of stone formation 20-30 years

Cystinuria; normal individuals excrete <100mg/day; heterozygote carriers excrete 150-300mg/day; homozygote affected individuals typically excrete >400mg/day (solubility limit ~250-300mg/day)

#### Investigation

Sodium nitroprusside spot test (Brandt's test)

Cystine + sodium cyanide = cysteine (pink)

Cysteine + nitroprusside = purple discolouration

Positive when urinary cystine > 75mg/L

False positives

Homocystinuria

Sulpha drugs

N-acetylcysteine

Ground glass appearance on plain film (disulphide bonds)

#### Medical management

High fluid intake (to produce 2.5 to 3 litres/day)

Limit sodium intake

Avoid red meat, fish and poultry (high levels of methionine – precursor of cystine)

Urinary alkaliisation (aim for pH 6.5-7.0 to improve solubility)

Cystine binders (disulphide bond to soluble drug cf. insoluble cystine)

(i) D-penicillamine (250mg/day: side effects nephrotic syndrome, dermatitis and pancytopenia; 70% cessation rate; rarely used)

(ii) Alpha mercaptopropionylglycine (aka Thiola; 100mg bd, titrated to urinary cystine < 250mg/day: better tolerated than penicillamine, but side effects asthenia, GI upset, rash; cessation rate 30%)

(iii) Captopril (no reported clinical trials – not currently recommended)

#### Other stones

##### a) Matrix stones

Mucoproteins and mucopolysaccharide

Radiolucent

Extremely rare

##### b) Bladder calculi

Migrant (from upper tracts)

Primary endemic

Children with low phosphate, cereal-based diets (low animal protein): high urinary ammonium and oxalate – typically ammonium urate +/- calcium oxalate

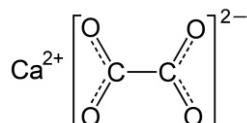
Secondary

BOO

- UTI
- Foreign body
- c) Drug associated stones
  - Stones made of drug
    - Indinavir HIV protease inhibitor
    - Triamterene K sparing diuretic
    - Guaifenesin
    - Ephedrine
    - Ciprofloxacin
  - Stones increasing risk of calcium stones
    - Bumetanide
    - Furosemide
    - Acetazolamide

## Appendix

### Chemical formulae



Calcium oxalate monohydrate (Whewellite) =  $\text{C}_2\text{H}_2\text{CaO}_5$

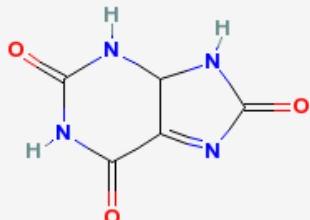
Calcium oxalate dihydrate (Weddellite) =  $\text{C}_2\text{H}_4\text{CaO}_6$

Tricalcium diphosphate (Hydroxyapatite) =  $\text{Ca}_3\text{O}_8\text{P}_2$

Calcium hydrogen phosphate dihydrate (Brushite) =  $\text{CaH}_5\text{O}_6\text{P}$

Magnesium ammonium phosphate (Struvite) =  $\text{H}_4\text{MgNO}_4\text{P}$

Carbonate apatite (Dahlite) =  $\text{Ca}_5(\text{PO}_4, \text{CO}_3)_3\text{F}$



Uric acid (above) =  $\text{C}_5\text{H}_4\text{N}_4\text{O}_3$

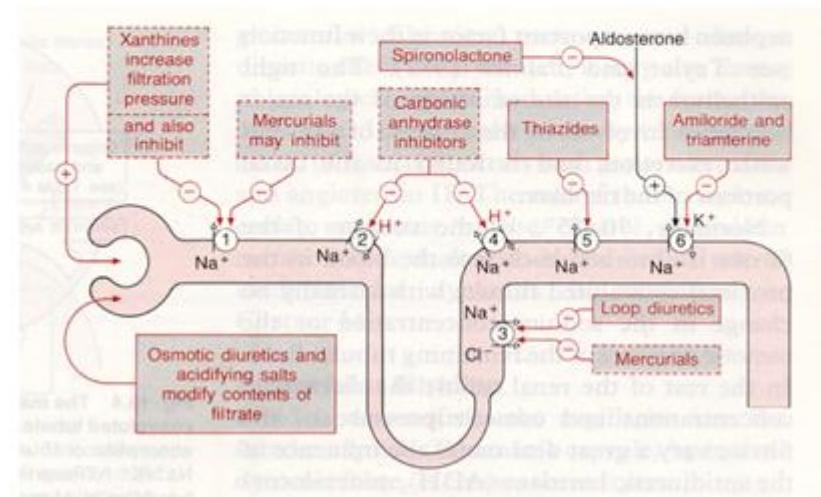
Ammonium urate =  $\text{C}_5\text{H}_7\text{N}_5\text{O}_3$

Sodium urate =  $\text{C}_5\text{H}_3\text{N}_4\text{NaO}_3$

### Renal physiology

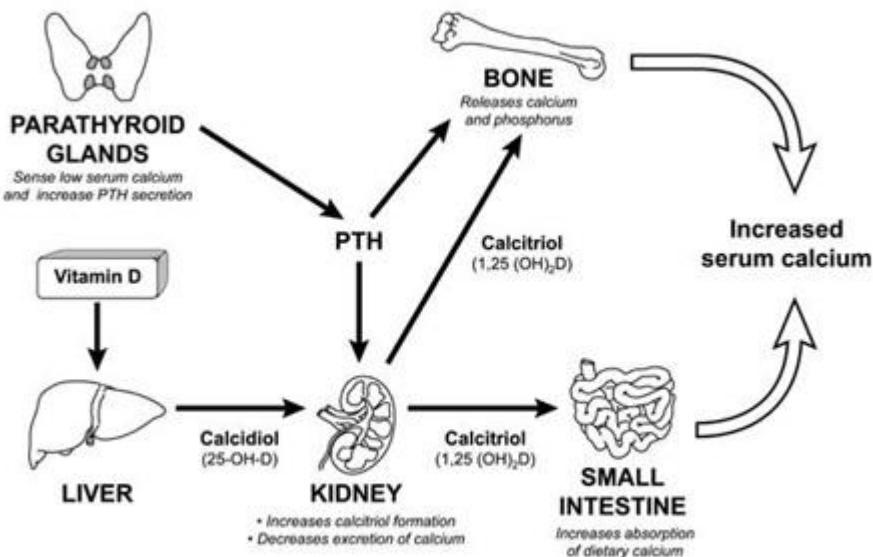
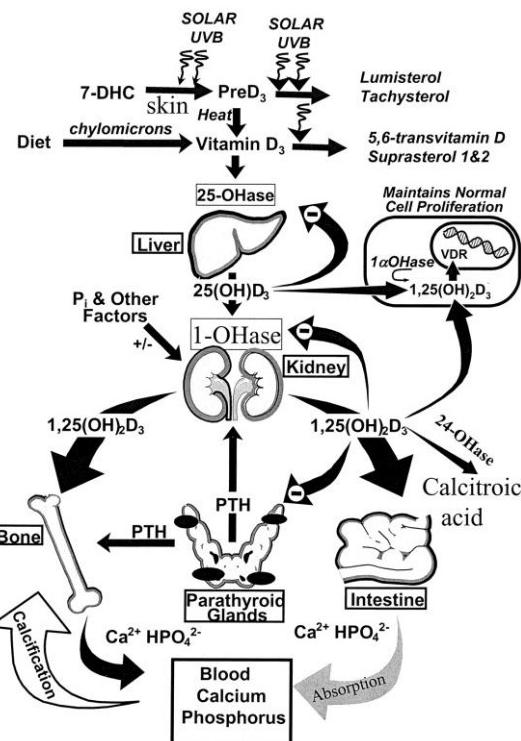
	Proximal nephron	LOH	Distal nephron
Na <sup>+</sup> reabsorption*	67%	25%	8%
Water reabsorption*	65%	15%	20%
Ca <sup>++</sup> reabsorption	65%	15%	15%
Mg <sup>++</sup> reabsorption	15%	60%	10%

\* maximum values



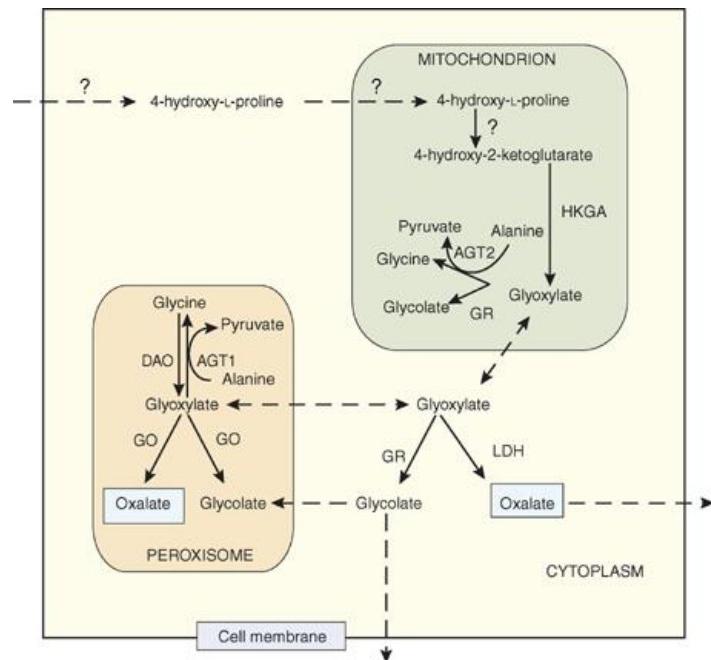
Calcium metabolism

40% dietary calcium absorbed; 90% small intestine, 10% colon  
 Only ionised non-complexed calcium absorbed, usually transcellular  
 When dietary calcium low, vitamin-D dependent channels increase fractional absorption

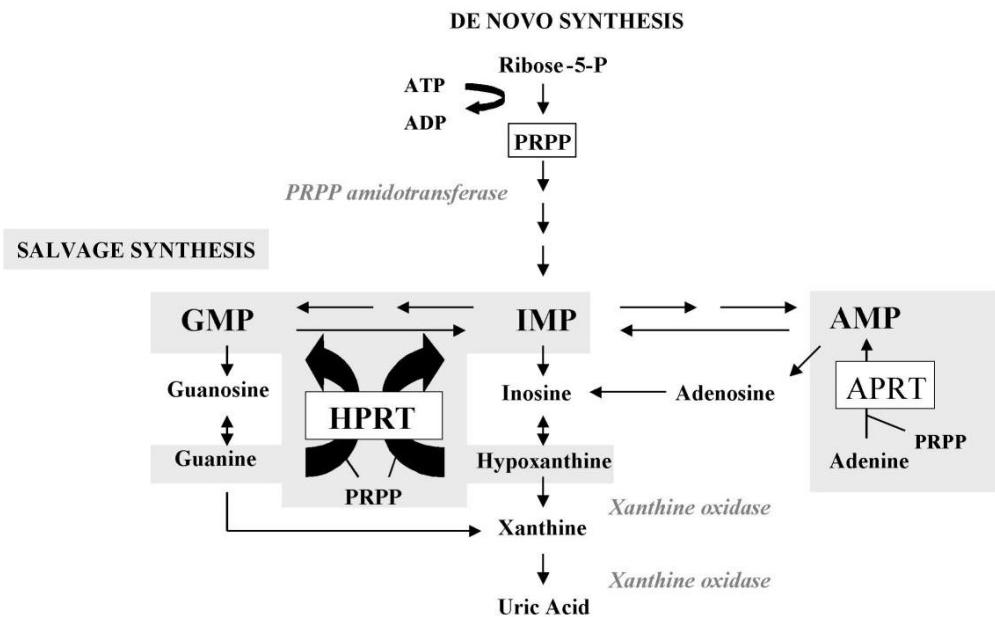
Vitamin D metabolismOxalate metabolism

Only 10-15% of ingested oxalate absorbed (50% small bowel; 50% colon)  
 May be significantly reduced in patients with enteric colonisation with *oxalobacter formigenes*. ? therapeutic benefit  
 Most oxalate appearing in urine from hepatic metabolism (50% glycine breakdown; 50% ascorbic acid breakdown)

Primary hyperoxaluria (type 1) caused by a deficiency of the hepatic enzyme alanine-glyoxylate aminotransferase (AGT). Results in failure of conversion of glyoxylate to glycine, leading to increased production of oxalic, glycolic and glyoxylic acids (see below)

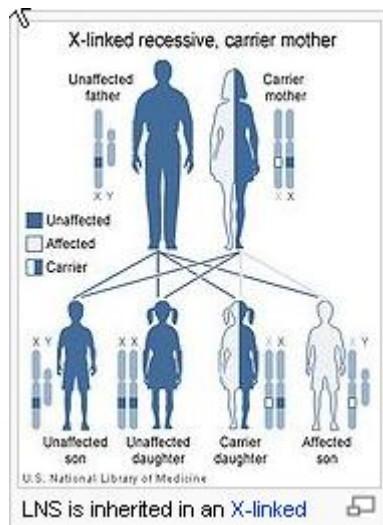


### Purine metabolism



HPRT = hypoxanthine-guanine phosphoribosyl transferase. Deficiency of HPRT seen in Lesch-Nyhan syndrome

Allopurinol – structural isomer of hypoxanthine; acts as xanthine oxidase inhibitor. High levels may be a/w formation of xanthine stones (hypoxanthine more soluble than xanthine)



### Renal tubular acidosis

Family of diseases characterized by failure of tubular H<sup>+</sup> secretion and urinary acidification:

- Type 1      Distal failure of H<sup>+</sup> secretion  
Diagnostic triad
  - Hyperchloraemic metabolic acidosis
  - High urinary pH (>5.5)
  - Low serum HCO<sub>3</sub>
 80% female; 70% form stones, typically calcium phosphate  
Associated low sodium, hyperaldosteronism, low potassium,  
Low citrate predisposes to calcium stone disease (especially calcium phosphate) – Rx with potassium citrate
- Type 2      Proximal failure of bicarbonate reabsorption  
Same triad as above, with low sodium and potassium  
Citrate normal - no stone disease  
Usually children - growth retardation and osteomalacia (Tiny Tim)
- Type 3      Actually type 1
- Type 4      Impaired distal H<sup>+</sup> and K<sup>+</sup> secretion. As above but with hyperkalaemia – therefore cannot treat with potassium citrate

Many patients with milder forms of disease not particularly acidotic. Single best test is ammonium chloride (100mg/Kg) urinary acidification test.  
Ammonium chloride dissociates into ammonium ions and H<sup>+</sup> ions – requires buffering by kidney. A urinary pH of <5.5 indicative of a failure of urinary acidification.

